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APPLICATION NUMBER: *60/144,106*
FILING DATE: *July 16, 1999*

PRIORITY DOCUMENT

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PTO/SB/16 (2-98)
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PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53 (c).

INVENTOR(S)

Given Name (first and middle [if any])	Family Name or Surname	Residence (City and either State or Foreign Country)
Marion	de Jong	The Netherlands

☐ *Additional inventors are being named on the ___ separately numbered sheets attached hereto*

TITLE OF THE INVENTION (280 characters max)

COMBINATION OF LYSINE AND ARGININE FOR REDUCTION OF KIDNEY UPTAKE OF PHARMACEUTICALS

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ENCLOSED APPLICATION PARTS *(check all that apply)*

[X] Specification *Number of Pages* 1 ☐ Small Entity Statement

☐ Drawing(s) *Number of Sheets* ___ ☐ Other (specify) ___

METHOD OF PAYMENT OF FILING FEES FOR THIS PROVISIONAL APPLICATION FOR PATENT *(check one)*

☐ A check or money order is enclosed to cover the filing fees

[X] The Commissioner is hereby authorized to charge filing fees or credit any overpayment to Deposit Account Number: 131160

FILING FEE AMOUNT ($): $150

The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

☐ No.

☐ Yes, the name of the U.S. Government agency and the Government contract number are: ______

Respectfully submitted,

SIGNATURE [signature]

Date 7/16/99

TYPED or PRINTED NAME Jeffrey S. Boone

REGISTRATION NO. *(if appropriate)* 29,284

TELEPHONE 314 654-8955

Docket Number: 1406 P

USE ONLY FOR FILING A PROVISIONAL APPLICATION FOR PATENT

1. Title of the invention : Combination of lysine and arginine for reduction of kidney reuptake of pharmaceuticals.

2. Brief Description of the Invention : Radio(metal)labeled peptides (and also monoclonal fragments and other compounds like certain antibiotics) undergo undesired renal reuptake and cellular retention, leading to a high kidney dose. Reduction of this re-uptake is possible using positively charged amino acids, L- and D-lysine being twice more effective than L-arginine in rat studies. In humans L-lysine was effective but at high doses it caused hyperkalemia in a number of patients. We found that the combination of L-lysine and L-arginine is significantly more effective at equimolar concentrations in reduction of kidney reuptake than both compounds alone.

3. Purpose of the Invention : To reduce kidney uptake of radiolabeled pharmaceuticals with such low doses of the combination of lysine and arginine (either in the L- or D-form) that the desired reduction of kidney uptake is achieved but kyperkalemia is prevented.

4. Detailed Description of the Invention : Radio(metal)labeled peptides (and also monoclonal fragments) undergo significant renal reuptake and cellular retention reducing the detection sensitivity of perirenal tumors and increasing kidney radiotoxicity during radionuclide therapy. We could reduce reuptake of the radiocompounds in the rat kidney in vivo: the most pronounced effects (50% inhibition of total kidney uptake) were obtained by D- and L-lysine (max effect achieved using 400 mg/kg). L-arginine gave a reduction of 20-30% at an equimolar dose. In human studies 15, 21 and 40% reduction of kidney uptake of $[^{111}\text{In-DTPA}^0]$octreotide was reached using a dose of 25, 50 and 75 g L-lysine, respectively. The doses of 25 and 50 g L-lysine were well tolerated without any toxicity noted. However, the 75 g L-lysine dose was associated with hyperkalemia in 60% of the patients, which may result in cardiotoxicity.

5. We have found that the combination of L-lysine and L-argine is more effective for reduction of kidney reuptake in rats than both compounds alone at equimolar concentrations. Using this combination, lower doses of the two amino acids can therefore effectively inhibit the (radio)pharmaceutical kidney reuptake and prevent hyperkalemia and cardiotoxicity.

6. Known References: 1) De Jong M, Rolleman EJ, Bernard BF, Visser TJ, Breeman WAP, Krenning EP. Inhibition of renal uptake of Indium-111-octreotide in vivo. J Nucl Med 37(8):1388-1392, 1996. 2) Bernard HF, Krenning EP, Breeman WAP, Rolleman EJ, Bakker WH, Visser TJ, Mäcke HR, De Jong M. D-lysine reduction of ^{111}In Octreotide and ^{90}Y Octreotide renal uptake. J Nucl Med 38:1929-1933, 1997.

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